

What is claimed is:

- 5 *Sum R1*
1. A method for making microspheres comprising a bioactive substance, the method comprising:

dissolving a polymer with an organic solvent to produce a polymer solution;

10 adding a biologically effective amount of a bioactive substance to the solution to produce a mixture of the polymer and the bioactive substance;

15 vibrating the mixture to produce a bioactive substance-polymer complex;

emulsifying the mixture to produce an emulsion comprising the bioactive substance-polymer complex; and

20 extracting the organic solvent from the emulsion to produce microspheres comprising the polymer-bioactive substance complex, wherein the bioactivity of the bioactive substance is usefully preserved.

25

2. The method of claim 1, wherein the microspheres are biodegradable and biocompatible.
3. The method of claim 1, wherein the bioactive substance comprises a therapeutic agent.
4. The method of claim 1, wherein the bioactive substance comprises a drug.
5. The method of claim 1, wherein the bioactive substance comprises a polypeptide.
6. The method of claim 1, wherein the bioactive substance is a solid.
7. The method of claim 1, wherein the bioactive substance is selected from the group consisting of nerve growth factor, interferon, growth hormone, insulin, erythropoietin, transforming growth factor, epidermal growth factor, interleukin-2, basic fibroblast growth factor and VEGF.
8. The method of claim 1, the method further comprising stabilizing the bioactive substance.

9. The method of claim 8, wherein the bioactive substance is stabilized with a carrier protein.

5 10. The method of claim 9, wherein the carrier protein comprises albumin.

11. The method of claim 8, wherein the bioactive substance is stabilized by maximizing the concentration of the substance in the solution, by adding a metal to the solution, by adding gelatin to the solution, or by adding a small osmolyte to the solution.

12. The method of claim 1, wherein the polymer comprises a combination of PLGA and PEG, wherein PEG comprises approximately 1% by weight of the combination.

13. The method of claim 1, wherein the organic solvent comprises methyl chloride.

14. The method of claim 1, wherein the mixture is emulsified with polyvinyl alcohol.

15. The method of claim 1, wherein the emulsion is extracted with polyvinyl alcohol and isopropyl alcohol.

16. The method of claim 1, the method further comprising removing the microspheres from the extracted emulsion.

5 17. The method of claim 16, wherein the microspheres are removed from the extracted emulsion by centrifugation.

18 The method of claim 16, the method further comprising washing, freezing and lyophilizing the removed microspheres,

10 19. A system for delivering a therapeutic agent to tissue, the system comprising:

15 biodegradable microspheres made according to the method of claim 1, wherein the microspheres comprise a therapeutic agent; and

20 a dispenser for administration of the microspheres to the tissue, whereby the microspheres release the therapeutic agent from the microspheres to the tissue.

25 20. The system of claim 19, wherein the release of the therapeutic agent from the microspheres occurs in two phases, the phases comprising an initial burst phase and a later steady-state phase.

21. A drug delivery system, the system comprising:

biodegradable microspheres made according to the method of claim 1, wherein the microspheres comprise a drug; and

a dispenser for administration of the microspheres.

22. The system of claim 21, wherein the microspheres release the drug in two phases subsequent to administration, the phases comprising an initial burst phase and a later steady-state phase.

23. A method for making microspheres comprising a solid bioactive substance, the method comprising:

dissolving a polymer with an organic solvent to produce a polymer solution;

adding a biologically effective amount of a solid bioactive substance to the solution to produce a mixture of the polymer and the bioactive substance;

vibrating the mixture to produce a bioactive substance-polymer complex;

emulsifying the mixture to produce an emulsion
comprising the bioactive substance-polymer complex;
and

extracting the organic solvent from the
emulsion to produce microspheres comprising the
polymer-bioactive substance complex, wherein the
bioactivity of the bioactive substance is usefully
preserved.

24. A method for microencapsulating a bioactive substance,
the method comprising:

providing a bioactive substance;

providing at least one polymer;

providing an organic solvent;

dissolving the polymer in a volume of the
organic solvent to produce a polymer solution;

adding the bioactive substance to the solution
to produce a mixture of the polymer and the
bioactive substance;

5

vibrating the mixture to produce a bioactive
substance-polymer complex;

10

emulsifying the mixture to produce an emulsion
comprising the bioactive substance-polymer complex;
and

15

extracting the organic solvent from the
emulsion to produce microspheres comprising the
polymer-bioactive substance complex, wherein the
biological activity of the bioactive substance is
substantially preserved.

25. ~~Microspheres made according to the method of claim 1.~~

20

26. The microspheres of claim 25, wherein the microspheres
are biodegradable.

27. The microspheres of claim 25, wherein the microspheres
comprise a therapeutic agent.

28. The microspheres of claim 27, wherein the therapeutic agent is selected from the group consisting of nerve growth factor, interferon, growth hormone, insulin, erythropoietin, transforming growth factor, epidermal growth factor, interleukin-2, basic fibroblast growth factor and VEGF.

29. The microspheres of claim 25, wherein the microspheres comprise a polypeptide.

30. The microspheres of claim 25, wherein the microspheres comprise a drug.

31. Microspheres made according to the method of claim 23.

32. The microspheres of claim 31, wherein the microspheres are biodegradable and biocompatible.

33. The microspheres of claim 31, wherein the microspheres comprise a therapeutic agent.

34. The microspheres of claim 33, wherein the therapeutic agent is selected from the group consisting of nerve

growth factor, interferon, growth hormone, insulin, erythropoietin, transforming growth factor, epidermal growth factor, interleukin-2, basic fibroblast growth factor and VEGF.

35. The microspheres of claim 23, wherein the solid bioactive substance comprises a polypeptide.
36. The microspheres of claim 23, wherein the microspheres comprise a drug.